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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/560,594

12/13/2005

Antonius Johannes Hendrikus Stegmann

2001-1418

7185

466

7590

08/18/2008

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EXAMINER

BLUMEL, BENJAMIN P

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/560,594	Applicant(s) STEGMANN ET AL.	
	Examiner BENJAMIN P. BLUMEL	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 1/4/08 & 5/30/08.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 6 and 11-13 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-5, 7-10 and 14-21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 13 December 2005 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/13/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION***Election/Restrictions***

Applicant's election without traverse of invention I and the required species in the replies filed on 1/4/08 & 5/30/08 is acknowledged.

Claims 6 and 11-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species and invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on January 4, 2008.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 12/13/05 was filed. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. However, the Dijkstra et al. reference only contains pages 1028 and 1029 not pages 1028-1036 as stated in the IDS.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Drawings

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because figures 4a, 4b, 5 and 7 refer to "present invention". Applicant is

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advised to employ the services of a competent patent draftsman outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7-10 and 19-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 7-10 and 19-21 recite, "...wherein the antigen is...", however, it is unclear where this antigen refers to the fusion protein of the virus (line 2 of claim 1) or the "further antigen" (line 3 of claim 1). Particularly since the elected species of influenza hemagglutinin (HA) of claim 10 is both a viral fusion protein and an antigen.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 14 and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Zurbriggen et al. (Progress in Lipid Research, 2000).

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The claimed invention is drawn to a pharmaceutical composition of a reconstituted viral membrane, the lipid bilayer comprising natural lipids of a viral membrane of which comprises a fusion protein of a virus, an amphiphilic adjuvant and, optionally, a further antigen, whereby:

(a) the lipid bilayer has a lipid composition that is compatible with fusion, induced by the fusion protein, of the viral membrane with the membrane of a cell that can be fused with the virus from which the fusion protein is derived;

(b) the fusion protein and the amphiphilic adjuvant interact with the hydrophobic interior of the lipid bilayer; and,

(c) the fusion protein, the amphiphilic adjuvant and the optional further antigen are not covalently linked.

Zurbriggen et al. teach a reconstituted influenza virosomes (IRIV) which contain lipids from influenza viral envelopes, and phosphatidylcholine (PC) and phosphatidylethanolamine (PE). The IRIV also contained influenza cell fusion protein hemagglutinin (HA), which traverses the bilayer and interacts with interior vesicle of the IRIV. The PE and PC also provide an adjuvant effect as part of the viral envelope, while interacting with both the inside and outside of the virosome. *See pages 3-6.* Therefore, the claimed invention is anticipated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-5 and 14-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stegmann (US PGPub 2005/0214359), Gluck and Metcalfe (Vaccine, 2003) and Zurbriggen et al. (*supra*).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention “by another”; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The claimed invention is drawn to a pharmaceutical composition of a reconstituted viral membrane, the lipid bilayer comprising natural lipids of a viral membrane of which comprises a fusion protein of a virus, an amphiphilic adjuvant and, optionally, a further antigen, whereby:

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(a) the lipid bilayer has a lipid composition that is compatible with fusion, induced by the fusion protein, of the viral membrane with the membrane of a cell that can be fused with the virus from which the fusion protein is derived;

(b) the fusion protein and the amphiphilic adjuvant interact with the hydrophobic interior of the lipid bilayer; and,

(c) the fusion protein, the amphiphilic adjuvant and the optional further antigen are not covalently linked. The amphiphilic adjuvant is the lipopeptide (N-palmitoyl-S-2,3(bisoleoyloxy)-propyl-cysteinyl-seryl-(lysyl)3-lysine) and is also a ligand for a mammalian (TLR) Toll-Like Receptor. This composition is suitable for intranasal, oral or parenteral administration.

Stegmann et al. teach both a reconstituted bilayer virosome and a co-micelle (non-bilayer) which contains influenza HA (a viral fusion protein). Stegmann et al. further teach that the HA and the adjuvant associate within the micelle. One example of such an amphiphilic lipoprotein adjuvant is that of N-palmitoyl-S-2,3(bisoleoyloxy)-propyl-cysteinyl-seryl-(lysyl)3-lysine. This lipoprotein is a ligand for TLR. These co-micelle compositions can be formulated for oral or intranasal administration. However, while Stegmann et al. do mention influenza virosomes, and their use in presenting antigens and fusing with target cells, they do not teach forming a bilayer viral membrane with a lipoprotein adjuvant traversing the membrane. *See paragraphs 11-15, 25, 28-31; examples 1, 3-6; and table 1.*

Gluck and Metcalfe teach the use of immunopotentiating reconstituted influenza virosomes (IRIVs), an empty bilayer molecule with contain intercalated influenza HA and NA on its surface. Gluck and Metcalfe discuss the adjuvant properties of IRIVs and

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their ability to target specific cells and fuse with them. Furthermore, when these IRIVs are administered with an adjuvant, a strong localized and systemic immune response is induced when administered intranasally. *See pages 611 and 614.*

The teachings of Zurbriggen et al. are discussed above.

It would have been obvious to one of ordinary skill in the art to modify the composition taught by Stegmann in order to use virosomes, instead of co-micelles in presenting viral fusion proteins and lipoprotein adjuvant. One would have been motivated to do so, given the suggestion by Stegmann that a virosome can also present viral fusion proteins along with other proteins. There would have been a reasonable expectation of success, given the knowledge that IRIVs can effectively fuse with target cells when HA is presented on the surface of the bilayer molecule and thereby introducing heterologous substances into the target cell and IRIVs function as adjuvants based on the presence of phospholipids in the membrane, as taught by Gluck and Metcalfe and Zurbriggen et al., and also given the knowledge that adding an external adjuvant to the IRIV enhances immune responses, as taught by Gluck and Metcalfe. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Summary

No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BENJAMIN P. BLUMEL whose telephone number is (571)272-4960. The examiner can normally be reached on M-F, 8-4:30.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stacy B Chen/
Primary Examiner, Art Unit 1648

/BENJAMIN P BLUMEL/
Examiner
Art Unit 1648